REMARKS

Rejection of Claims and Traversal Thereof

In the June 13, 2002 Office Action,

claims 14-61, 65 and 66 were rejected under 35 U.S.C. §103 (a) as being unpatentable over Donnelly, et al. (WO 96/00583) and Johnson (U.S. Patent No. 5,658,785) in further view of Whittle, et al. (U.S. Patent No. 5,658,785);

claims 16, 18, 20 and 50 were rejected under 35 U.S.C. §103 (a) as being unpatentable over Donnelly, et al. (WO 96/00583), Johnson (U.S. Patent No. 5,658,785) and Whittle, et al. (U.S. Patent No. 5,658,785) in further view of Gissmann, et al. (WO 96/11272); and

claim 61 was rejected under 35 U.S.C. §103 (a) as being unpatentable over Donnelly, et al. (WO 96/00583), Johnson (U.S. Patent No. 5,658,785) and Whittle, et al. (U.S. Patent No. 5,658,785) in further view of Stanley, et al. (U.S. Patent No. 6,096,869).

These rejections are hereby traversed and reconsideration of the patentability of the pending claims is requested in light of the following remarks.

Rejection under 35 U.S.C. §103 (a)

In the June 13, 2002 Office Action, claims 14-61, 65 and 66 were rejected under 35 U.S.C. §103 (a) as being unpatentable over Donnelly, et al. and Johnson in further view of Whittle, et al. Applicants submit that Donnelly, et al. in combination with Johnson and Whittle, et al. does not render applicants' claimed invention *prima facte* obvious.

The present invention relates to an adeno-associated virus vector comprising a nucleotide sequence encoding a fusion polypeptide. The fusion polypeptide comprises a structural papillomavirus polypeptide and **an early non-transforming** papillomavirus polypeptide having the C-terminus of

the structural polypeptide connected to the N-terminus of the early **non-transforming** early polypeptide. The connection between the structural and **non-transforming** early polypeptide is produced by ligating the 3' end of the structural ORF to the 5' end of the **non-transforming early ORF** thereby encoding for the connected fusion polypeptide. The presently claimed invention specifically includes a **non-transforming early ORF**, which as described on the top of page 4 of the present specification, refers to the fact that the polypeptide has no transformation ability by nature or through intervention. Transformation is clearly described in the present specification as the conversion of a normal cell into a tumor cell which has the capacity for unlimited proliferation. Thus, the presently claimed invention, by using **only non-transforming early ORFs, eliminates the ability of extracellular DNA from recombining with the cell genome, to prevent giving the cells new genetic properties**.

In the June 13, 2002 Office Action, the Office stated that:

> "while Donnelly et al. and Johnston teach the expression of multivalent antigens of both early and late ORFs of papillomavirus, neither reference provides the specific teaching to combine the various proteins, or fragments thereof, into one fusion protein comprising both an early ORF and a late ORF. Lacking the specific teaching to combine the proteins into one fusion protein, the teachings of Donnelly et al. and Johnson do not make obvious the instantly claimed invention, and the rejection is withdrawn."

By the above statement, it is clear that the Office recognizes that the combination of Donnelly, et al. and Johnson does not establish a *prima facie* case of obviousness. However, the Office mistakenly believes that the combination is only lacking in the teaching of fusion proteins and has failed to address the fact that **Donnelly et al. teaches away from using the viral vectors of Johnson.**

Johnson relates to a eukaryotic expression system comprising recombinant Adeno-Associated Virus (AVV) vectors that are used in combination with a helper virus for transfection of cells. Viral vectors, especially AAV, cause integration of the AAV genome and any foreign DNA material included in the AAV genome into the chromosomic material of the transfected cell. Because of this integration directly into the DNA of the cell, AAV exhibits long-term gene

expression *in vivo*. Thus, genes transfected by the AAV, whether detrimental to the subject or not, are expressed by the transfected cell.

According to the Office, as stated at page 4 in the June 13, 2002 Office Action, Donnelly, et al. teaches that "generally any appropriate vector can be used for delivery of papillomavirus ORF sequences." Applicants vigorously disagree because Donnelly, et al. expressly teaches the use of **artificially engineered plasmids.** Clearly, Donnelly, et al **teaches away** from the use of viral vectors, such as those described by Johnson to infect cells, because as stated at page 4, in the first full paragraph of the Donnelly, et al. reference:

> "Retroviral vectors have restriction on the size and structure of polypeptides that can be expressed as fusion proteins while maintaining the ability of the recombinant virus to replicate, and the effectiveness of vectors such as vaccinia for subsequent immunization may be compromised by immune responses against the vectors themselves. Also viral vectors and modified pathogens have inherent risk that may hinder their use in humans."

Further, Donnelly, et al., expressly states, at the bottom of page 5, that using the described engineered plasmid DNA is **advantageous because no assembly of virus particles is required and no infectious agent is involved.** Thus, Donnelly, et al. explicitly teaches away from using a viral vector such as described by Johnson, mainly for the reason that Johnson teaches that a virus helper is required for transfection (see column 4, line 41). It should be further noted that Donnelly, et al, does not in any way discuss, teach or suggest using only **non-transforming early E6-ORF or E7-ORF** for inclusion in the described **artificially engineered plasmids.** Clearly, the Donnelly, et al. reference is completely silent regarding transformation of transfected cells because the engineered plasmids described by Donnelly, et al. provide no mechanism for integration of the virus DNA into the cell genome.

Thus understood, applicants request that the Office explain why one skilled in the art, after reading the above quoted sections of Donnelly, et al., would consider using a viral vector which requires the use of a virus helper, such as that taught by Johnson, for transfection of a cell. Clearly, one reading the Johnson reference , which expressly states that a virus helper is required for

transfection, and then Donnelly, et al., which teaches the disadvantage of using a virus helper, would not think of combining the two references, with or without Whittle, et al.

To overcome the shortcomings of the Donnelly, et al. and Johnson combination, the Office introduced Whittle, et al. which describes fusion proteins comprising late and early ORFs. However, it is evident that Whittle, et al. does not include any additional teachings that in combination with Donnelly, et al. and Johnson establish a *prima facie* case of obviousness.

As stated above, the presently claimed invention comprises a fusion polypeptide that combines a late structural ORF or fragments thereof and a **non-transforming** E6-ORF or E7-ORF or fragments thereof for inclusion into an AAV viral vector system.

According to the Office:

> "Whittle, et al. teach that at the time of filing many of the ORFs have been used for the production of HPV vaccines (see columns 1-3), and provide specific and necessary guidance to generate polynucleotide sequences which encode fusion proteins comprising late and early ORFs of papillomavirus."

Applicants insist that Whittle, et al. does not in way describe, teach or suggest the presently claimed invention.

According to MPEP 706.02(j):

> "To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir 1991)."

Firstly, the Office has not identified any objective or specific teachings or suggestions in the cited references that would motivate one skilled in the art to combine the references. According to the Office, "the test for combining references is not what the individual references themselves suggest, but rather what the combination of disclosures taken as a whole would have suggested to one of ordinary skill in the art" (see page 6 of June 13, 2002 Office Action wherein the Office cited a 1971 decision by the CCPA (*In re McLaughlin*, 170 USPQ 209)). Applicants take issue with the cited case law because the cited references in McLaughlin did not present conflicting construction, such as in the present instance. If the Office insists that the references must be taken as a whole then the fact that Donnelly, et al. and Whittle, et al. both teach away from using the viral vector system of Johnson must also be considered. Clearly, Donnelly, et al. teaches away from using viral vectors, and thus one skilled in the art would not consider combining Donnelly, et al. with Johnson, with or without Whittle, et al. Furthermore, Whittle, et al teaches away from using eukaryotic expression systems because of the low yield and instead prefers the use of a prokaryotic expression system. Thus, one would not consider combining the eukaryotic expression system of Johnson with the teaching of Whittle, et al., with or without Donnelly, et al.

The Office should be aware that the Federal Circuit recently addressed the question whether there is a reason to combine references and what is required by the examiner to show a suggestion to combine references and stated: (See *In re Lee*, 61 USPQ3d 1430, 1433 (Fed. Cir. 2002))

> "'The factual inquiry whether to combine references must be thorough and searching.' *Id.* It must be based on **objective evidence of record**. This precedent has been reinforced in myriad decisions, and **cannot** be dispensed with. *See, e.g., Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 229 F.3d 1120, 1124-25, 56 USPQ2d 1456, 1459 (Fed. Cir. 2000) ("a showing of a suggestion, teaching, or motivation to combine the prior art references is an 'essential component of an obviousness holding'") (quoting *C.R. Bard, Inc., v. M3 Systems, Inc.*, 157 F.3d 1340, 1352, 48 USPQ2d 1225,1232 (Fed. Cir. 1998)); *In re Dembiczak*, 175 F.3d 994, 999, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999) ("Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-**based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references**."); *In re Dance*, 160 F.3d 1339, 1343, 48 USPQ2d 1635, 1637 (Fed. Cir. 1998) (there must be some motivation, **suggestion,** or teaching of **the desirability** of making the specific combination that was made by the applicant); *In re Fine*, 837 F.2d 1071, 1075, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988) ("'teachings of references can be combined *only* if there is some suggestion or incentive to do so.'") (emphasis in original) (quoting *ACS Hosp. Sys., Inc. v. Montefiore Hosp.*, 732 F.2d 1572, 1577, 221 USPQ 929, 933 (Fed. Cir. 1984)).

> **The need for specificity pervades this authority**. *See, e.g., In re Kotzab*, 217 F.3d 1365, 1371, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000) ("particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected **these components for combination in the manner claimed**"); *In re Rouffet*, 149 F.3d 1350, 1359, 47 USPQ2d 1453, 1459 (Fed. Cir. 1998) ("even when the level of skill in the art is high, the Board must identify specifically the principle, known to one of ordinary skill, that suggests the claimed combination.
>
> In other words, the Board must explain the reasons one of ordinary skill in the art would have been motivated to select the references and to combine them to render the claimed invention obvious."); *In re Fritch*, 972 F.2d 1260, 1265, 23 USPQ2d 1780, 1783 (Fed. Cir. 1992) (the examiner can satisfy the burden of showing obviousness of the combination "**only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references**")." (Emphasis added)

Reading the above quote, it is apparent that the Federal Circuit in 2002 has raised the bar that the Office must meet to show a suggestion or motivation to combine references to establish a *prima facie* case of obviousness, relative to the 1971 case cited by the Office. Applicants submit that the Office has not met the current standard set forth by the Federal Circuit to show a suggestion or motivation to combine the cited references.

Secondly, in light of the fact that both Donnelly, et al. and Whittle, et al. teach away from using the eukaryotic viral vector system of Johnson, there is no reasonable expectation of success. Not one of the fusion proteins described in Whittle, et al. has been introduced into a eukaryotic expression system because Whittle, et al. expressly states that a eukaryotic system generates a low expression level and teaches away from uses an eukaryotic expression system. Accordingly, there is no suggestion or teaching for the combination proposed by the Office.

Thirdly, even if all the references were combinable, which they are not, the combination still does not in any way disclose, teach or suggest each and every limitation of the presently claimed invention. Specifically, neither Donnelly, et al. nor Whittle, et al., either alone or with Johnson teach or suggest a **fused polypeptide** comprising a structural papillomavirus polypeptide encoded by an open reading frame selected from the group consisting of L1-ORF, L2-ORF and fragments of any of the foregoing ORFs; and a **non-transforming** early E6-ORF, E7-ORF and fragments of any of the foregoing ORFs. Donnelly, et al. is completely silent relating to the inclusion of **non-transforming** E6-ORF and E7-ORF in the described engineered plasmids. Of course, Donnelly, et

al. **does not use viral vectors, as discussed above, and thus integration of the early transforming genes into the cell genome is not recognized as a problem.** Likewise, Whittle, et al. does not in any way, disclose, teach or suggest using non-transforming E6-ORF or E7-ORF genes for inclusion in the prokaryotic expression system described in Whittle, et al. Thus, the proposed combination by the Office, does not meet **all** the requirements set forth in the MPEP, as required to establish a *prima facie* case of obviousness.

In light of the above discussion and the fact that (1) there is no motivation, suggestion or teaching to combine the references; (2) each and every recited limitation of applicants' claimed invention is not disclosed or suggested in the cited references; and (3) even if the references were combinable, which they are not, Donnelly, et al. and Whittle, et al. teach away from use of a viral vector such as that disclosed in the Johnson reference; it is clear that the cited combination fails to establish a *prima facie* case of obviousness of applicants' claims as herein amended.

Claims 16, 18, 20 and 50 were rejected under 35 U.S.C. §103 (a) as being unpatentable over Donnelly, et al., Johnson and Whittle, et al. in further view of Gissmann, et al. Regardless, of the teachings of Gissmann, et al., applicants respectfully submit that the defects in the alleged *prima facie* case over Donnelly, et al., Johnson and Whittle, et al. are not cured by the addition of Gissmann, et al.

The Office must view Gissmann, et al. in its entirety and if properly viewed, the cited reference in combination with the primary and secondary references still does not teach or suggest all the claimed limitations of the present invention. Gissmann, et al. discloses fused polypeptides wherein a portion of a viral structural proteins of HPV, whether L1 or L2, is deleted. In the deleted area of the sequence another sequence is inserted. This is in sharp contrast to Donnelly, et al. that expressly states that maintaining the conserved portions of the papilloma viruses, such as structural portions L1 and L2, is important to provide protection against subsequent challenges by different types of papilloma viruses. Donnelly, et al. maintains the integrity of the structural proteins for the specific reason of providing extended protection, even if a subsequent attack occurs by another virus strain. Clearly, mutating the L1 or L2 structural gene is precluded by Donnelly, et al. and as such the Gissmann, et al and Donnelly, et al. references are not combinable.

More important, if the mutation of L1 and L2 as taught by Gissmann, et al. is introduced into the DNA constructs of Donnelly, et al. the intended purpose of maintaining a highly conserved structural protein in the Donnelly, et al. reference is destroyed. Thus, there is no motivation to combine the cited references and the Office has not provided any teachings or suggestions sufficient to provide one skill in the art the motivation to make the proposed modifications needed to arrive at applicants' claimed invention.

Claim 61 was rejected under 35 U.S.C. §103 (a) as being unpatentable over Donnelly, et al., Johnson and Whittle, et al. in further view of Stanley, et al. Regardless of the teachings of Stanley, et al. applicants respectfully submit that the defects in the alleged prima facie case over Donnelly, et al., Johnson and Whittle, et al. are not cured by the addition of Stanley, et al. Thus, for the reasons set forth above, this rejection also is improper.

In light of the foregoing observations and the clarifying amendments to the claims, applicants submit that the cited references fail to suggest the subject matter of the rejected claims. Reconsideration and withdrawal of the rejections is respectfully requested.

Petition for Extension of Time/Fees Payable

The applicants hereby petition for a one (1) month extension of time, extending the deadline for responding to the June 13, 2002 Office Action from September 13, 2002 to October 13, 2002. The entry of this petition results in a petition fee of $55.00. A check in the amount of $55.00 is submitted herewith in payment of the petition fee for a one-month extension. The U.S. Patent and Trademark Office is hereby authorized to charge any additional amount necessary to the entry of this amendment, and to credit any excess payment, to Deposit Account No. 08-3284 of Intellectual Property/Technology Law.

Conclusion

Applicants have satisfied the requirements for patentability. All pending claims are free of the art and fully comply with the requirements of 35 U.S.C. §112. It therefore is requested that Examiner Woitach reconsider the patentability of claims 14-61, 65-66, in light of the distinguishing remarks

herein and withdraw all rejections, thereby placing the application in condition for allowance. Notice of the same is earnestly solicited. In the event that any issues remain, Examiner Andres is requested to contact the undersigned attorney at (919) 419-9350 to resolve same.

Respectfully submitted,

Marianne Fuierer
Registration No. 39,983
Attorney for Applicant

INTELLECTUAL PROPERTY/
TECHNOLOGY LAW
P.O. Box 14329
Research Triangle Park, NC 27709
Telephone: (919) 419-9350
Fax: (919) 419-9354
Attorney Ref: 4121-107 RCE 2

APPENDIX A

In the Claims

Please amend claims 14, 38-50 and 65 as follows:

14. (Thrice Amended) An adeno-associated virus vector comprising a nucleotide sequence encoding a fusion polypeptide, the fusion polypeptide comprising:

a structural papillomavirus polypeptide encoded by an open reading frame selected from the group consisting of L1-ORF, L2-ORF and fragments of any of the foregoing ORFs; and

an early papillomavirus polypeptide encoded by an open reading frame selected from the group consisting of: [E1-ORF, E2-ORF, E4-ORF, E5-ORF,] E6-ORF, E7-ORF and fragments of any of the foregoing ORFs, wherein said early papillomavirus polypeptides or fragments thereof are non-transforming, and wherein the 3' end of the structural ORF is ligated to the 5' end of a non-transforming ORF to encode for the fusion polypeptide having a C-terminus of the structural polypeptide connected to a N-terminus of the non-transforming polypeptide.

38. (Amended) The vector of claim 14, wherein the early papillomavirus polypeptide is encoded by non-transforming E6-ORF.

39. (Amended) The vector of claim 14, wherein the early papillomavirus polypeptide is encoded by a fragment of non-transforming E6-ORF.

40. (Amended) The vector of claim 14, wherein the early papillomavirus polypeptide is encoded by non-transforming E7-ORF.

41. (Amended) The vector of claim 14, wherein the early papillomavirus polypeptide is encoded by a fragment of non-transforming E7-ORF.

42. (Amended) The vector of claim 14, wherein the early papillomavirus polypeptide is encoded by HPV 16 non-transforming E6-ORF.

43. (Amended) The vector of claim 14 wherein:
the early papillomavirus polypeptide is encoded by non-transforming E6-ORF or a fragment thereof; and
structural papillomavirus polypeptide is encoded by L2-ORF or a fragment thereof.

44. (Amended) The vector of claim 14 wherein:
the early papillomavirus polypeptide is encoded by HPV 16 non-transforming E7-ORF or a fragment thereof; and
structural papillomavirus polypeptide is encoded by HPV 16 L2-ORF or a fragment thereof.

45. (Amended) The vector of claim 14 wherein:
the early papillomavirus polypeptide is encoded by HPV 16 non-transforming E6-ORF or a fragment thereof; and
structural papillomavirus polypeptide is encoded by HPV 16 L2-ORF or a fragment thereof.

46. (Amended) The vector of claim 14 wherein:
the early papillomavirus polypeptide is encoded by HPV 16 non-transforming E7-ORF or a fragment thereof; and
structural papillomavirus polypeptide is encoded by HPV 16 L2-ORF or a fragment thereof.

47. (Amended) The vector of claim 14 wherein:
the early papillomavirus polypeptide is encoded by HPV 18 non-transforming E6-ORF or a fragment thereof; and
structural papillomavirus polypeptide is encoded by HPV 18 L2-ORF or a fragment thereof.

48. (Amended) The vector of claim 14 wherein:
the early papillomavirus polypeptide is encoded by HPV 18 non-transforming E7-ORF or a fragment thereof; and

structural papillomavirus polypeptide is encoded by HPV 18 L2-ORF or a fragment thereof.

49. (Thrice Amended) An adeno-associated virus vector comprising a nucleotide sequence encoding a fusion polypeptide, the fusion polypeptide comprising:

a structural human papillomavirus polypeptide encoded by an open reading frame selected from the group consisting of L1-ORF and L2-ORF; and

an early human papillomavirus polypeptide encoded by an open reading frame selected from the group consisting of: [E1-ORF, E2-ORF, E4-ORF, E5-ORF,] E6-ORF and E7-ORF, wherein said early human papillomavirus polypeptides are non-transforming, and wherein the 3' end of the structural ORF is ligated to the 5' end of a non-transforming ORF to encode for the fusion polypeptide having a C-terminus of the structural polypeptide connected to a N-terminus of the non-transforming polypeptide.

50. (Thrice Amended) An adeno-associated virus vector comprising a nucleotide sequence encoding a fusion polypeptide, the fusion polypeptide comprising:

a structural human papillomavirus polypeptide encoded by an open reading frame selected from the group consisting of L1-ORF and L2-ORF; and

an early human papillomavirus polypeptide encoded by an open reading frame selected from the group consisting of: [E1-ORF, E2-ORF, E4-ORF, E5-ORF,] E6-ORF and E7-ORF, wherein said early human papillomavirus peptides are non-transforming, and wherein the 3' end of the structural ORF is ligated to the 5' end of a non-transforming ORF to encode for the fusion polypeptide having a C-terminus of the structural polypeptide connected to a N-terminus of the non-transforming polypeptide, and the human papillomavirus of (a) and (b) is selected from the group consisting of HPV 16, HPV 18, HPV 33, HPV 35 and HPV 45.

65. (Thrice Amended) A method for activating an immune system of a subject comprising administering to the subject an adeno-associated virus vector comprising a nucleotide sequence encoding a fusion polypeptide, the fusion polypeptide comprising:

a structural papillomavirus polypeptide encoded by an open reading frame selected from the group consisting of: L1-ORF, L2-ORF and fragments of any of the foregoing ORFs; and

an early papillomavirus polypeptide encoded by an open reading frame selected from the group consisting of: [E1-ORF, E2-ORF, E4-ORF, E5-ORF,] E6-ORF, E7-ORF and fragments of any of the foregoing ORFs, wherein said early papillomavirus polypeptides are non-transforming, and wherein the 3' end of the structural ORF is ligated to the 5' end of a non-transforming ORF to encode for the fusion polypeptide having a C-terminus of the structural polypeptide connected to a N-terminus of the non-transforming polypeptide.

APPENDIX B

All pending claims

14. (Thrice Amended) An adeno-associated virus vector comprising a nucleotide sequence encoding a fusion polypeptide, the fusion polypeptide comprising:

a structural papillomavirus polypeptide encoded by an open reading frame selected from the group consisting of L1-ORF, L2-ORF and fragments of any of the foregoing ORFs; and

an early papillomavirus polypeptide encoded by an open reading frame selected from the group consisting of: E6-ORF, E7-ORF and fragments of any of the foregoing ORFs, wherein said early papillomavirus polypeptides or fragments thereof are non-transforming, and wherein the 3' end of the structural ORF is ligated to the 5' end of a non-transforming ORF to encode for the fusion polypeptide having a C-terminus of the structural polypeptide connected to a N-terminus of the non-transforming polypeptide.

15. The vector of claim 14, wherein the structural papillomavirus polypeptide is an HPV polypeptide.

16. The vector of claim 15, wherein the HPV is selected from the group consisting of HPV 16, HPV 18, HPV 33, HPV 35 and HPV 45.

17. The vector of claim 14, wherein the early papillomavirus polypeptide is an HPV polypeptide.

18. The vector of claim 17, wherein the HPV is selected from the group consisting of HPV 16, HPV 18, HPV 33, HPV 35 and HPV 45.

19. The vector of claim 14 wherein, both the structural papillomavirus polypeptide and the early papillomavirus polypeptide are HPV polypeptides.

20. The vector of claim 19, wherein the HPV is selected from the group consisting of HPV 16, HPV 18, HPV 33, HPV 35 and HPV 45.

21. The vector of claim 14, wherein the nucleotide sequence is under the control of a constitutive promoter.

22. The vector of claim 14, wherein the nucleotide sequence is under the control of an inducible promoter.

23. The vector of claim 14, wherein the nucleotide sequence is under the control of a tissue-specific promoter.

24. The vector of claim 14, wherein the nucleotide sequence is under the control of a tumor-specific promoter.

25. The vector of claim 14, wherein the structural papillomavirus polypeptide is encoded by L1-ORF.

27. The vector of claim 14, wherein the structural papillomavirus polypeptide is encoded by L2-ORF.

29. The vector of claim 14, wherein the structural papillomavirus polypeptide is encoded by HPV 16 L1 ORF.

38. (Amended) The vector of claim 14, wherein the early papillomavirus polypeptide is encoded by non-transforming E6-ORF.

39. (Amended) The vector of claim 14, wherein the early papillomavirus polypeptide is encoded by a fragment of non-transforming E6-ORF.

40. (Amended) The vector of claim 14, wherein the early papillomavirus polypeptide is encoded by non-transforming E7-ORF.

41. (Amended) The vector of claim 14, wherein the early papillomavirus polypeptide is encoded by a fragment of non-transforming E7-ORF.

42. (Amended) The vector of claim 14, wherein the early papillomavirus polypeptide is encoded by HPV 16 non-transforming E6-ORF.

43. (Amended) The vector of claim 14, wherein:
the early papillomavirus polypeptide is encoded by non-transforming E6-ORF or a fragment thereof; and
structural papillomavirus polypeptide is encoded by L2-ORF or a fragment thereof.

44. (Amended) The vector of claim 14 wherein:
the early papillomavirus polypeptide is encoded by HPV 16 non-transforming E7-ORF or a fragment thereof; and
structural papillomavirus polypeptide is encoded by HPV 16 L2-ORF or a fragment thereof.

45. (Amended) The vector of claim 14 wherein:
the early papillomavirus polypeptide is encoded by HPV 16 non-transforming E6-ORF or a fragment thereof; and
structural papillomavirus polypeptide is encoded by HPV 16 L2-ORF or a fragment thereof.

46. (Amended) The vector of claim 14 wherein:
the early papillomavirus polypeptide is encoded by HPV 16 non-transforming E7-ORF or a fragment thereof; and
structural papillomavirus polypeptide is encoded by HPV 16 L2-ORF or a fragment thereof.

47. (Amended) The vector of claim 14 wherein:

the early papillomavirus polypeptide is encoded by HPV 18 non-transforming E6-ORF or a fragment thereof; and
structural papillomavirus polypeptide is encoded by HPV 18 L2-ORF or a fragment thereof.

48. (Amended) The vector of claim 14 wherein:
the early papillomavirus polypeptide is encoded by HPV 18 non-transforming E7-ORF or a fragment thereof; and
structural papillomavirus polypeptide is encoded by HPV 18 L2-ORF or a fragment thereof.

49. (Thrice Amended) An adeno-associated virus vector comprising a nucleotide sequence encoding a fusion polypeptide, the fusion polypeptide comprising:

a structural human papillomavirus polypeptide encoded by an open reading frame selected from the group consisting of L1-ORF and L2-ORF; and

an early human papillomavirus polypeptide encoded by an open reading frame selected from the group consisting of: E6-ORF and E7-ORF, wherein said early human papillomavirus polypeptides are non-transforming, and wherein the 3' end of the structural ORF is ligated to the 5' end of a non-transforming ORF to encode for the fusion polypeptide having a C-terminus of the structural polypeptide connected to a N-terminus of the non-transforming polypeptide.

50. (Thrice Amended) An adeno-associated virus vector comprising a nucleotide sequence encoding a fusion polypeptide, the fusion polypeptide comprising:

a structural human papillomavirus polypeptide encoded by an open reading frame selected from the group consisting of L1-ORF and L2-ORF; and

an early human papillomavirus polypeptide encoded by an open reading frame selected from the group consisting of: E6-ORF and E7-ORF, wherein said early human papillomavirus peptides are non-transforming, and wherein the 3' end of the structural ORF is ligated to the 5' end of a non-transforming ORF to encode for the fusion polypeptide having a C-terminus of the structural

polypeptide connected to a N-terminus of the non-transforming polypeptide, and the human papillomavirus of (a) and (b) is selected from the group consisting of HPV 16, HPV 18, HPV 33, HPV 35 and HPV 45.

51. (Twice Amended) An adeno-associated virus vector comprising a nucleotide sequence encoding a fusion polypeptide, the fusion polypeptide comprising:

a structural human papillomavirus polypeptide encoded by L1-ORF or a fragment thereof; and

an early human papillomavirus polypeptide encoded by an open reading frame selected from the group consisting of: E6-ORF, E7-ORF and fragments of any of the foregoing ORFs, wherein said early human papillomavirus polypeptides are non-transforming, and wherein the 3' end of the structural ORF is ligated to the 5' end of a non-transforming ORF to encode for the fusion polypeptide having a C-terminus of the structural polypeptide connected to a N-terminus of the non-transforming polypeptide.

52. (Twice Amended) An adeno-associated virus vector comprising a nucleotide sequence encoding a fusion polypeptide, the fusion polypeptide comprising:

a structural human papillomavirus polypeptide encoded by an HPV16 or 18 L1-ORF or a fragment thereof; and

an early human papillomavirus polypeptide encoded by an HPV 16 or 18 open reading frame selected from the group consisting of E6-ORF, E7-ORF and fragments of any of the foregoing ORFs, wherein said early human papillomavirus polypeptides are non-transforming, and wherein the 3' end of the structural ORF is ligated to the 5' end of a non-transforming ORF to encode for the fusion polypeptide having a C-terminus of the structural polypeptide connected to a N-terminus of the non-transforming polypeptide.

53. (Twice Amended) An adeno-associated virus vector comprising a nucleotide sequence encoding a fusion polypeptide, the fusion polypeptide comprising:

a structural human papillomavirus polypeptide encoded by HPV16 or 18 L1-ORF; and

an early human papillomavirus polypeptide encoded by an HPV 16 or 18 open reading frame selected from the group consisting of: E6-ORF and E7-ORF, wherein said early papillomavirus polypeptides are non-transforming, and wherein the 3' end of the structural ORF is ligated to the 5' end of a non-transforming ORF to encode for the fusion polypeptide having a C-terminus of the structural polypeptide connected to a N-terminus of the non-transforming polypeptide.

54. The vector of claim 53, wherein the ORFs of (a) and (b) are HPV 16 ORFs.

55. The vector of claim 53, wherein the ORFs of (a) and (b) are HPV 18 ORFs.

56. The vector of claim 53 wherein:
the ORFs of 53(a) and 53(b) are HPV 16 ORFs; and
the early human papillomavirus polypeptide is encoded by E6-ORF.

57. The vector of claim 53 wherein:
the ORFs of 53(a) and 53(b) are HPV 18 ORFs; and
the early human papillomavirus polypeptide is encoded by E6-ORF.

58. The vector of claim 53 wherein:
the ORFs of 53(a) and 53(b) are HPV 16 ORFs; and
the early human papillomavirus polypeptide is encoded by E7-ORF.

59. The vector of claim 53 wherein:
the ORFs of 53(a) and 53(b) are HPV 18 ORFs; and
the early human papillomavirus polypeptide is encoded by E7-ORF.

60. A vaccine composition comprising:
the vector of claim 14; and

an auxiliary agent.

61. The vaccine composition of claim 49, further comprising one or more immune system-activating agents.

65. (Thrice Amended) A method for activating an immune system of a subject comprising administering to the subject an adeno-associated virus vector comprising a nucleotide sequence encoding a fusion polypeptide, the fusion polypeptide comprising:

a structural papillomavirus polypeptide encoded by an open reading frame selected from the group consisting of: L1-ORF, L2-ORF and fragments of any of the foregoing ORFs; and

an early papillomavirus polypeptide encoded by an open reading frame selected from the group consisting of: E6-ORF, E7-ORF and fragments of any of the foregoing ORFs, wherein said early papillomavirus polypeptides are non-transforming, and wherein the 3' end of the structural ORF is ligated to the 5' end of a non-transforming ORF to encode for the fusion polypeptide having a C-terminus of the structural polypeptide connected to a N-terminus of the non-transforming polypeptide.

66. The method of claim 65, wherein the fusion polypeptide is administered as a component of a vaccine composition.